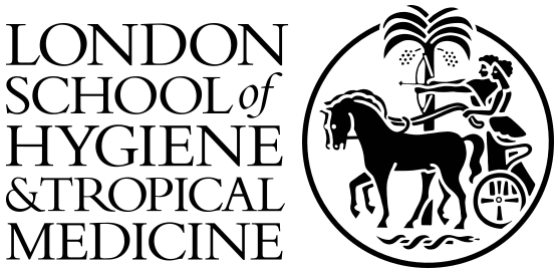

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The risk of non-specific hospitalised infections following MMR vaccination given with and without inactivated vaccines in the second year of life. Comparative self–controlled case-series study in England

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ABSTRACT

Observational cohort studies in high-income settings have suggested that vaccination order may affect children's subsequent risk of a heterologous infection, with live vaccines reducing and inactivated vaccines (given on their own or with a live vaccine), increasing the risk. We used the self-controlled case-series method, which automatically controls for the individual level confounding to which such cohort studies are prone, to test this hypothesis. We compared the relative incidence (RI) of infections post-vaccination in two calendar periods in England; in Period 1 (September 2002–August 2006) live measles, mumps, rubella (MMR) vaccine was given on its own and in Period 2 (September 2006–April 2010) inactivated vaccines (7-valent pneumococcal conjugate vaccine (PCV7) and sometimes the combined *Haemophilus influenzae* type b/meningococcal group C vaccine (Hib-MenC)) were given concomitantly with MMR. Admissions for an infection of the upper or lower respiratory tract, gastrointestinal system or other site in children aged 11–23 months were selected from the Hospital Episode Statistics database in England and linked to child health immunisation histories. The analysis included a total of 24,144 infections in 21,067 children in Period 1 and 36,880 in 31,616 children in Period 2. The RI of admission for any infection in Period 1 was 1.00 (95% confidence interval 0.95–1.06) compared with 0.95 (95% confidence interval 0.90–1.00) in Period 2. Comparing the two periods showed no evidence of a difference in the relative incidence estimates with a ratio of RI of 0.94 (95% confidence interval 0.87–1.02), RIs within 90 days of vaccination were 0.94 (0.91–0.97) in Period 1 and 0.94 (0.91–0.97) in Period 2, consistent with a temporary healthy vaccinee effect. In conclusion, we found no evidence to support the hypothesis that there is a reduction in heterologous infections after MMR on its own or an increase after MMR given concomitantly with an inactivated vaccine.

1. Background

Some studies suggest that vaccines can have non-specific effects on the immune system such that they change the risk of contracting unrelated infections that are not targeted by the vaccine. Studying such non-specific effects is more complex than assessing the specific vaccine effect because of the large number of possible diseases to examine, unclear biological mechanism and likelihood of finding false associations by chance or through study bias and confounding.

Studies reporting non-specific effects have focused on overall mortality largely in a small number of low income countries in West Africa [1,2] and, more recently, in high-income countries on heterologous infections [3,4,5]. Some of these studies have reported beneficial effects for live vaccines such as measles and BCG and deleterious effects for inactivated vaccines such as the combined diphtheria, tetanus, pertussis vaccine (DTP), with stronger effects often seen in girls than boys. A specific hypothesis raised and assessed in these studies is that receiving an inactivated vaccine with or after a live vaccine is detrimental relative to receiving live vaccine on its own as the last vaccine in a sequence [4,5,6].

A recent systematic review of largely observational cohort studies with a mortality outcome found that, while there was some evidence to support non-specific effects, most were subject to a substantial risk of bias [1,2]. Similarly, bias has been demonstrated in studies with heterologous infections as the outcome in high income settings [7]. Since such observational studies rely on differ-

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ences between children in the order or timing in which vaccines are given they are particularly prone to confounding arising from individual differences in health status or socio-economic variables that determine both the exposure and outcome. Use of the self-controlled case-series (SCCS) method which automatically controls for such individual differences would provide an ideal method for controlling for such bias [8].

In England we have previously used the SCCS method to examine the hypothesis that administration of three live viral vaccines combined - measles, mumps and rubella (MMR) – might "overload the immune system", at a time when calls were made for single antigen vaccines during the time of the erroneous MMR and autism safety concerns [9]. We subsequently reported no increase in hospitalisations for either bacterial or viral infections following MMR in the second year of life but found an apparent protective effect in the 30 days post MMR [10]. Since this study was done two inactivated vaccines have been added to the UK schedule, a combined *Haemophilus influenzae type* b/Meningococcal group C (Hib-MenC) vaccine given as a booster and a 7-valent pneumococcal conjugate vaccine (PCV7) given as two priming doses in infancy with a later booster. These two booster vaccines were recommended to be given either at the same time as, or for Hib-MenC, prior to MMR. Using the SCCS method, we have therefore updated our previous study to test the hypothesis that the risk of heterologous infections is higher when MMR is given with an inactivated vaccine than on its own.

2. Methods

2.1. Design

The study design was a self-controlled case-series [8] in which the relative incidence of hospitalised infections in a time period when MMR vaccine was given alone is compared to a period when MMR was given with PCV7 or with both PCV7 and the combined Hib-MenC vaccine. This comparative SCCS method has been used previously to compare reactions following acellular and whole cell pertussis vaccines [11] and is depicted in Fig. 1.

2.2. Case selection

We defined cases as children aged 11 to 23 months with a hospital admission in England (based on national hospital episode statistics (HES) data [12]) for an infection during the period 01/09/2002 and 30/04/2010 that were linked on NHS number to vaccine data from the Careplus child health immunisation system (CHIS), representing approximately 20% of the population in England. The areas using CHIS were geographically dispersed and included 17 of the 152 Primary Care Trusts across the country, covering parts of the South, South-West, Midlands and North-West of England. We identified infections based on ICD codes in any of the 20 HES diagnostic fields (supplementary Table S1) and grouped them into all infections, upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), gastrointestinal infections (gastro) and other infections (other). These codes covered those used previously [8,9] with additional codes similar to those used by Sorup et al, encompassing a wide range of bacterial and viral infections (excluding infections that are commonly vertically transmitted, or that are characterised by a longer incubation period such as Mycobacterium tuberculosis) [3]. Where more than one event was coded on the same day we used the event in the earliest diagnostic field. We excluded events occurring within 14 days of a previous event as these were likely to be part of the same infection episode. To facilitate capture of ongoing infection episodes, we extracted events from birth to 23 months before restriction to 11 to 23 months.

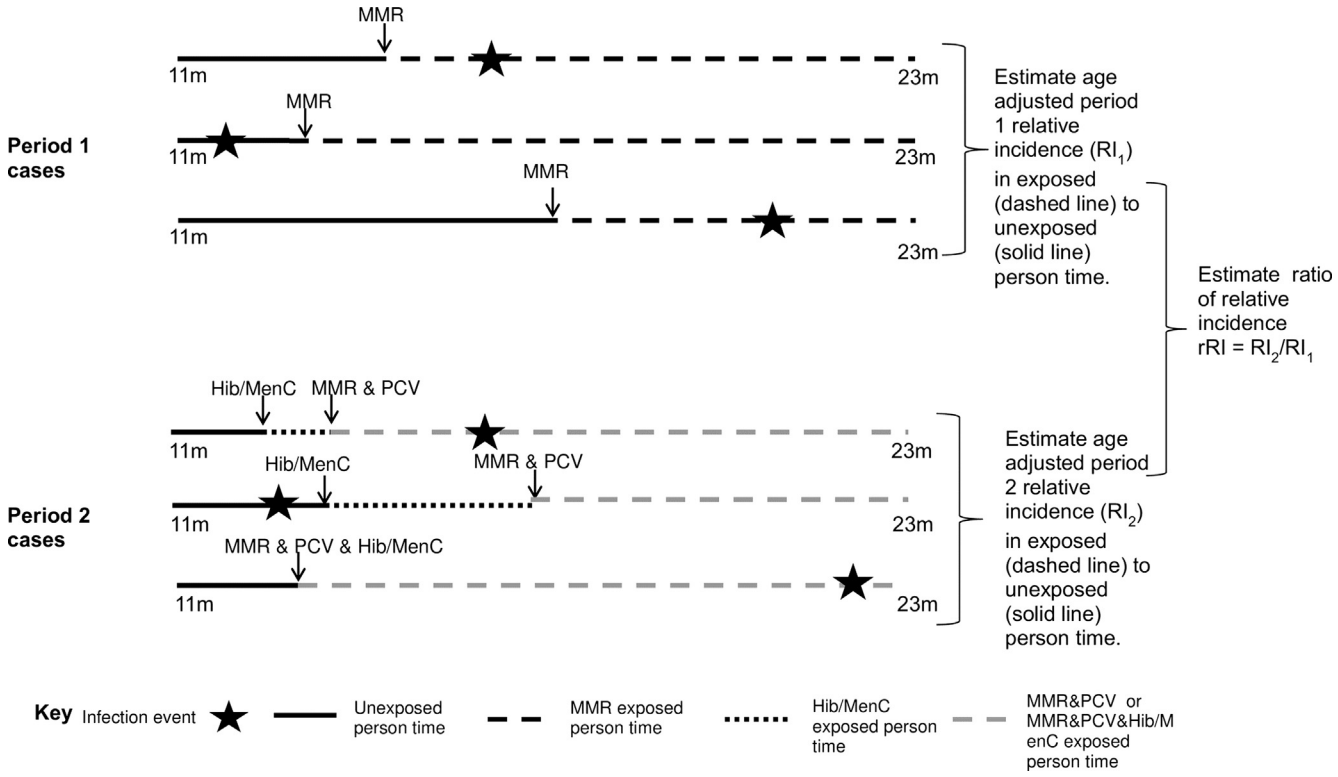

Fig. 1. Schematic showing the self-controlled case-series method for estimating the ratio of relative incidence (rRI) between the two periods with examples of person time for 3 cases in each period.

2.3. Exposure

After linkage to the CHIS data we only retained those cases with a record of MMR given from age 11–23 months. Cases whose MMR vaccination was between September 2002 and August 2006 were allocated to Period 1 and those whose MMR vaccination was between September 2006 and April 2010 were allocated to Period 2. These two periods reflect those in which MMR was scheduled to be given on its own (Period 1) and with PCV7 and sometimes Hib-MenC (Period 2). We chose the overall study period to coincide with CHIS data availability and to have a similar length with each schedule. The end of Period 2 also coincided with the change from PCV7 to the13-valent PCV in September 2010. For Period 1 we only retained individuals who received MMR vaccine and no other vaccine aged 11–23 months. For Period 2 we only retained individuals who received MMR with PCV7. We also dropped cases in Period 2 if they received other vaccines with the exception of Hib-MenC which they could have either at the same time as MMR and PCV7 or prior to MMR and PCV7, but not after. The vaccine schedule used in England across the study period is shown in supplementary Table S2. We did not make any selection based on receipt of primary vaccinations, but almost all children will have received the recommended primary infant schedule comprising DTP-containing vaccines given with MenC, and in Period 2 also with PCV7. Children are called for vaccination at around the recommended age in England by an appointment letter, with reminders sent for non-attenders. Age at MMR vaccination for the CHIS overall and those with the same vaccine inclusion and exclusion criteria as used for the study populations in Period 1 and 2 was similar (supplementary Fig. S1).

2.4. Statistical methods

The hypothesis being tested was that the relative incidence of infections following MMR alone was the same as when MMR was given with PCV7 or with PCV7 and Hib-MenC. In testing this hypothesis, we also, as a secondary aim, tested the hypotheses that infection incidence is the same following each of the vaccinations compared to the period prior to MMR or prior to Hib-MenC if this was given earlier than MMR. The SCCS method uses a conditional Poisson model to estimate the relative incidence (RI) within individuals of the outcome of interest (here, hospitalised infections) in designated post-vaccination risk intervals compared to person-time outside these intervals. The post-vaccination risk window we chose was (a) any time (up to age 23 months) after MMR vaccination, and (b) within 90 days following MMR vaccination. In Period 2 those who received a Hib-MenC vaccine prior to MMR/PCV7 had an additional risk interval extending from the date of Hib-MenC to the day before MMR/PCV7. The period outside the risk windows comprised person time before vaccination for the analysis looking at RI at any time post vaccination, and, in addition, person time beyond 90 days for the analysis looking at the 90-day risk window. To estimate the ratio of RI (rRI) between the two time periods, we created an indicator variable for the Period (1 or 2) and then estimated the interaction term of this with the post-MMR risk time (Fig. 1). We adjusted for age using thirteen 28 day intervals and one 31 day interval by including it as a factor in the model. We only included person time from 11 to 23 months of age because prior to 11 months MMR and Hib-MenC vaccines are not given and infection rates change with age which would mean person time at an earlier age would be uninformative. Since the age of vaccination varied little over the study period we did not expect confounding by season (calendar month) or year (September-August from 2002/03 to 2009/2010), but we did check for this in the main analyses assessing relative incidence at any time after vaccination. To assess effect modification by gender we assessed whether the RI estimates differed by gender for each period using an interaction term. In sensitivity analyses we, (i) excluded infection codes that may have a component that is attributable to measles, mumps, rubella, pneumococcal, *Haemophilus influenza* b or meningococcal C infection for which there could be a protective effect of MMR, Hib-MenC or PCV vaccines, (ii) used weekly age adjustment and, (iii) just included in Period 2 those who received MMR/PCV7 and Hib-MenC on the same day. All analyses were done in Stata version 13 [StataCorp, College Station, TX].

3. Results

Fig. 2 shows how cases were selected for inclusion in the study. The final number of hospitalisations was 24,144 infection episodes in 21,067 children for Period 1 and 36,880 infection episodes in 31,616 children for Period 2. The average follow-up time per individual was 395 days in period 1 and 360 days in period 2. Of the 31,616 children, 29,410 had Hib-MenC in Period 2, of whom 1,100 had Hib-MenC at the same time as MMR and PCV7 and 28,310 received Hib-MenC before MMR/PCV7. The numbers of each event grouping in each period used in the SCCS analyses are shown in Table 1 along with the gender of the individuals and age. Events were more common in boys and decreased fairly uniformly with age, although more rapidly in Period 2.

The results of the SCCS analysis are shown in Table 2. Following MMR given on its own (Period 1) the RI of infections did not differ from unity, with the exception of a small decreased risk when restricting to the window within 90 days of MMR receipt. When MMR was given with PCV7 (Period 2) the RI also did not differ from unity with the exception of the 90-day risk window for all infections and a 21% decreased risk of a LRTI at any time post- vaccination before 24 months of age. Comparing the two periods showed no evidence of a difference in the RI estimates post-MMR for any analysis. In the second period the relative incidence post Hib-MenC was also close to one but, as with in the period shortly after MMR, the relative incidence was just below one for all infections in the interval between Hib-MenC and MMR and for LRTI where there was a 12% decreased risk. In the sensitivity analysis, excluding infections for which there may be a specific effect of vaccination led to dropping 1314 episodes in Period 1 and 1567 in Period 2, most of which were LRTI episodes (1154 and 1338 in Period 1 and 2 respectively). The "all infections" results remained similar but the reductions post vaccination for LRTI events in Period 2 became less and non-significant (Table 3). Results were similar when adjusting for age weekly (Table 3). Furthermore, adjusting for year within each period or for calendar month did not change relative incidence estimates for all events post MMR by more than 5% so these time-varying factors were not included in the models. There was no evidence of effect modification on the post-MMR RI by gender in either period (ratio of RI in males vs. females = 0.98 (95% confidence interval (CI): 0.92–1.04, p = 0.43) for Period 1 and 1.01 (95%CI: 0.96–1.07, p = 0.64) for Period 2).

4. Discussion

In this paper we have used the self-controlled case-series method, which eliminates bias arising from individual confounding factors that affect both exposure and outcome, to test whether the RI of infections following vaccination differs if MMR is given with inactivated vaccines (PCV7 and sometimes Hib-MenC) compared with on its own. From other studies [4,5] the hypothesised direction of the RI would be that it is greater if MMR is given with inactivated vaccines and we find no evidence to support this. None of the RIs for Period 2 when MMR was given with PCV7 were significantly different from those in Period 1 when MMR was given on

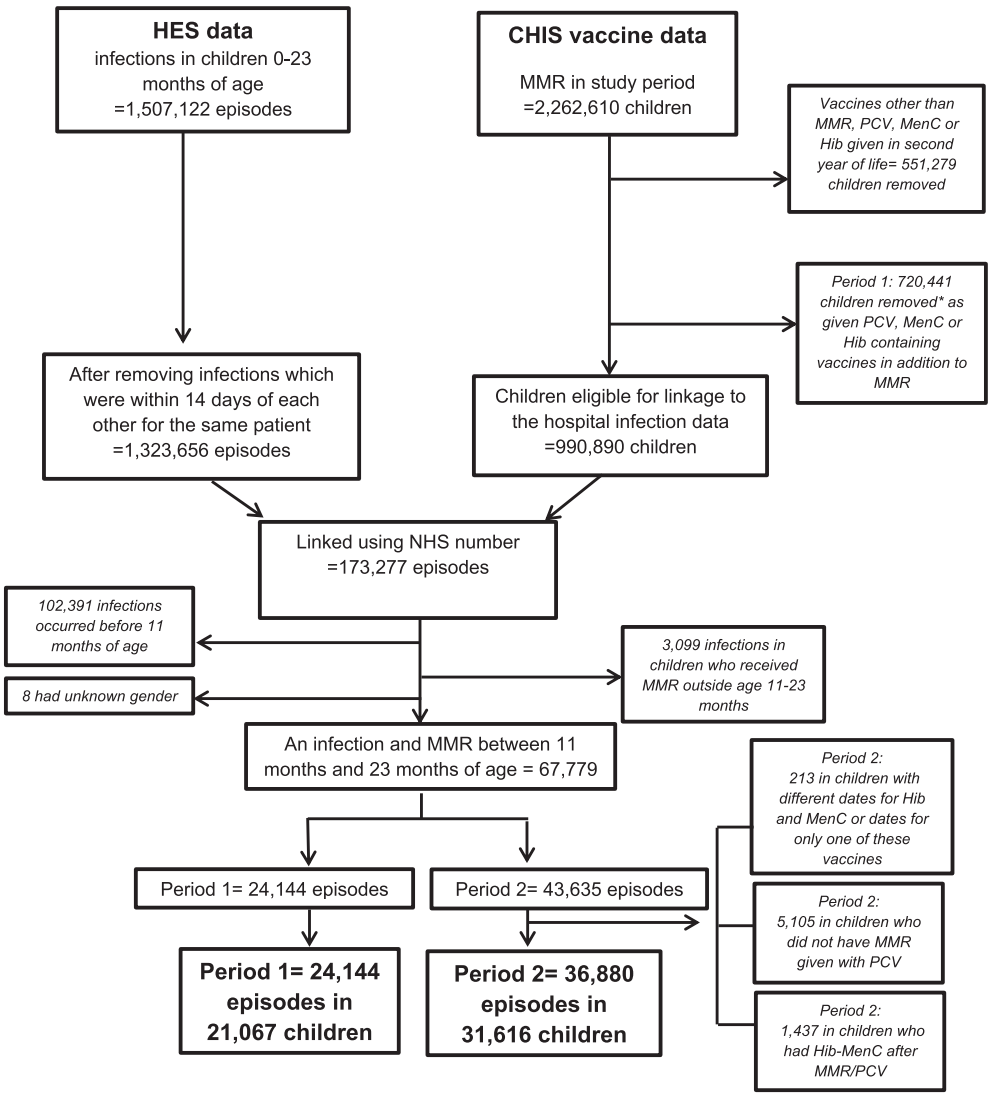

Fig. 2. Data linkage and selection of infection episodes for analysis.

its own. There was no evidence of an increased risk of infections after any vaccination nor of any gender-specific differences, nor that MMR on its own decreased the subsequent risk of a heterologous infection in the second year of life.

The 5–6% reduction in all-cause infections within 90 days of MMR given either alone or concomitantly with PCV7, or in the short interval between Hib-MenC and MMR/PCV7, is consistent with a temporary healthy vaccinee effect caused by children being more likely to be taken for vaccination when they are well than when incubating an illness. This temporary healthy vaccine effect has been previously documented in the week after MMR vaccine or a placebo in a randomised double-blind study [13] and also in the week after DTP vaccine with either a whole cell or acellular pertussis component where the relative incidence of diarrhoea was ~25% lower when combining estimates together from day 0 to 8 after vaccine [11]. In a post-hoc analysis we separately looked at the period a week after vaccination and found significant 25–30% reductions in infections in this week, which when removed from the 90 day period post MMR increased the RI in the remaining 8–90 day periods for all infections from 0.94 to 0.96 (95% CI: 0.93–1.00) for period 1 and from 0.94 to 0.98 (0.95–1.01) for period 2.

The 21% reduction in LRTI admissions at any time after MMR/PCV7 in the main analysis (Table 2) was larger and lasted longer than would be expected to be due to a temporary healthy vaccinee effect. However, in the sensitivity analysis where we excluded codes that may have a pneumococcal-attributable component this reduction became non-significant, consistent with a specific protective effect of PCV7 (Table 3). The majority of the excluded codes in the LRTI category were lobar pneumonia many of which in young children are likely to be caused by the pneumococcus [14]. The 12% reduction in LRTIs between Hib-MenC and MMR/PCV7 also became non-significant when potential vaccine-preventable codes were excluded.

Our results do not confirm the results of studies conducted in Denmark by Sorup et al [3,4] using a national linked database and cohort methodology and with a DTaP-containing vaccine as the exemplar of an inactivated vaccine. In the study evaluating the effect of MMR given after or with DTaP-IPV-HIB [4] the major-

Table 1
Description of infection events included in the analysis by period.

Factor	Level	Period1 MMR only (N = 24,144)	Period2 MMR with PCV7 (N = 36,880)
Infection Category	Gastrointestinal	5092	7858
	LRTI	3361	5053
	URTI	9043	12,817
	Other	6648	11,152
Gender	Female	10,655	16,233
	Male	13,489	20,647
Age (4 week intervals)	335 to 362 days	2137	3848
	363 to 390 days	2099	3666
	391 to 418 days	2049	3512
	419 to 446 days	1865	3332
	447 to 474 days	1945	3095
	475 to 502 days	1850	2873
	503 to 530 days	1768	2652
	531 to 558 days	1609	2435
	559 to 586 days	1621	2319
	587 to 614 days	1591	2064
	615 to 642 days	1422	1961
	643 to 670 days	1453	1804
	671 to 698 days	1305	1572
	699 to 730 days	1430	1747

LRTI = lower respiratory tract infections; URTI = upper respiratory tract infections

ity of children received the vaccines in the recommended order – three doses of DTaP-IPV-Hib in the first year of life followed by MMR with a small minority receiving the third DTaP-IPV-Hib with or sometimes after MMR. An increase in the risk of hospital admission for a LRTI but not other types of infection (eg URTI) was found for children who received simultaneous MMR and DTaP-IPV-Hib as their last vaccine compared with those whose last vaccine was MMR. Adjustment for available clinical, demographic and socioeconomic variables reduced the incidence rate ratio (IRR) for LRTIs from 1.58 (95%CI: 1.41–1.77) to 1.27 (1.13 to 1.42). This raises the possibility that, despite the adjustment for the available variables, residual bias or confounding from unmeasured variables may still be present. In an earlier paper [3] using the same Danish data set but just comparing children who received the recommended sequence of vaccines with those who received the third dose of DTaP-IPV-Hib after MMR (4% of the study cohort), the biggest effect was seen for URTIs between 11 and 23 months of age with an adjusted IRR for DTaP-IPV-Hib as the last vaccine compared to MMR of 1.89 (95%CI: 1.30 – 2.76). Thus, the putative non-specific effects are not consistent within the same birth cohort and appear to be sensitive to the follow up period chosen.

In the US study using a database of health insurance claims, the more generic hypothesis was tested, namely that the risk of non-targeted infections after a live vaccine is lower than after an inactivated vaccine given with or without a live vaccine [5]. Cohort methodology was used with adjustment for available clinical and geographical variables and with follow up from 16 to 24 months of age. In addition to MMR and DTaP the study cohort was eligible to receive five inactivated vaccines (hepatitis A or B, PCV7, polio and Hib) and varicella as an additional live vaccine, given with or separately from MMR. Although MMR was recommended to be given between 12 and 15 months of age and DTaP between 15 and 18 months, for the other live and attenuated vaccines there was no recommended schedule that if followed would have ensured that one or other vaccine was given last. The adjusted analyses showed a lower risk of any infection when a live vaccine was the last administered compared with an inactivated vaccine, hazard ratio 0.50 (95%CI: 0.43–0.57) with a smaller effect if the live vaccine was given concurrently with an inactivated vaccine, hazard ratio 0.78 (95%CI: 0.67–0.91); unadjusted hazard ratios were not presented. However, the factors that determine when or if a child receives a particular vaccine at a particular time in a complex

Table 2
SCCS analysis of the relative incidence of infections following MMR vaccination given on its own (Period 1) or with PCV7 (Period 2), and following Hib-MenC vaccination (Period 2).

Events	Period 1 Vaccine (risk window)	Period 1 events	Period1 RI (95% CI)	Period 2 Vaccine (risk window)	Period 2 events	Period 2 RI (95% CI)	Period 2:Period1 rRI (95% CI)
All				Hib-MenC (to MMR/PCV7)	6017	0.94 (0.90–0.98)	
	MMR (to age 23 m)	16,127	1.00 (0.95–1.06)	MMR/PCV7* (to age 23 m)	22,078	0.95 (0.90–1.00)	0.94 (0.87–1.02)
All				Hib-MenC (to MMR/PCV7)	6017	0.94 (0.90–0.97)	
	MMR (within 90 days)	5671	0.94 (0.91–0.97)	MMR/PCV7* (within 90 days)	8903	0.94 (0.91–0.97)	1.00 (0.95–1.05)
Gastro				Hib-MenC (to MMR/PCV7)	1316	0.99 (0.89–1.09)	
	MMR (to age 23 m)	3279	0.93 (0.83–1.04)	MMR/PCV7* (to age 23 m)	4621	0.92 (0.81–1.04)	0.99 (0.84–1.17)
URTI				Hib-MenC (to MMR/PCV7)	2032	0.97 (0.90–1.05)	
	MMR (to age 23 m)	6289	1.06 (0.97–1.15)	MMR/PCV7* (to age 23 m)	7959	1.05 (0.96–1.16)	1.00 (0.88–1.13)
LRTI				Hib-MenC (to MMR/PCV7)	859	0.88 (0.78–0.99)	
	MMR (to age 23 m)	2122	0.95 (0.83–1.09)	MMR/PCV7* (to age 23 m)	2788	0.79 (0.68–0.91)	0.83 (0.68–1.01)
Other				Hib-MenC (to MMR/PCV7)	1810	0.90 (0.83–0.98)	
	MMR (to age 23 m)	4437	1.02 (0.92–1.12)	MMR/PCV7* (to age 23 m)	6710	0.93 (0.84–1.03)	0.92 (0.80–1.05)

RI = relative incidence; rRI = ratio of relative incidences.
* Also given with Hib-MenC for about 3% of vaccinations.

Table 3
SCCS analysis of the relative incidence of infections following MMR vaccination given on its own (Period 1) or with PCV7 (Period 2), and following Hib-MenC vaccination (Period 2). Sensitivity analysis results.

Analysis*	Period 1 Vaccine (risk window)	Period 1 events	Period1 RI (95% CI)	Period 2 Vaccine (risk window)	Period 2 events	Period2 RI (95% CI)	Period2:Period1 rRI (95% CI)
Possible vaccine preventable infections excluded	MMR (to age 23 m)	15,227	1.01 (0.96–1.06)	Hib-MenC (to MMR/PCV7)	5777	0.95 (0.91–1.00)	
				MMR/PCV7** (to age 23 m)	21,145	0.96 (0.91–1.02)	0.96 (0.89–1.03)
LRTI events, Possible vaccine preventable infections excluded	MMR (to age 23 m)	1327	0.95 (0.81–1.12)	Hib-MenC (to MMR/PCV7)	649	0.96 (0.84–1.10)	
				MMR/PCV7** (to age 23 m)	1996	0.87 (0.73–1.03)	0.91 (0.72–1.15)
Age adjusted using weekly intervals	MMR (to age 23 m)	16,127	1.01 (0.96–1.06)	Hib-MenC (to MMR/PCV7)	6017	0.93 (0.89–0.98)	
				MMR/PCV7** (to age 23 m)	22,078	0.94 (0.89–1.00)	0.93 (0.87–1.01)
Just those in period 2 getting all 3 vaccines together	MMR (to age 23 m)	16,127	1.00 (0.95–1.06)	MMR/PCV7/Hib-MenC only (to age 23 m)	2110	1.02 (0.91–1.15)	1.02 (0.90–1.15)

* The default model has all events included, 4-week age adjustment, follow up to 23 months with risk window to the end of follow-up, all pre-vaccination person time included in the control period and no exclusion of possible vaccine component infections.
** Also given with Hib-MenC for about 3% of vaccinations. RI = relative incidence; rRI = ratio of relative incidence.

schedule such as that in the US are not known and are unlikely to be completely controlled for by variables included in the adjusted analyses. Thus, as stated by the authors themselves "the extent of potential biases from confounding and selection bias is unknown".

Caution in the interpretation of observational studies which rely on children in the same birth cohort receiving vaccines for unknown reasons in different sequences or at different ages was advised by the authors of a population based cohort study in the Netherlands [7]. The recommended schedule in the study was DTaP-IPV-Hib at 2, 3, 4 and 11 months followed by MMR given at the same time as the inactivated meningococcal C conjugate vaccine (MenC) at 14 months. The hazard ratio for the risk of an admission for an infection adjusted for a range of infant, parental and household variables when MMR and MenC vaccines were given last compared with when the last dose was the fourth DTaP-IPV-Hib was 0.62 (95% CI: 0.57–0.67) consistent with a higher risk after a DTaP-containing vaccine. However, there was also a reduced risk of infection when children who had received their fourth dose of DTaP-IPV-Hib vaccine were compared with those who at a similar age had only received a third dose. This suggests that timely receipt of a recommended dose may be a marker of a child with a generally more healthy constitution, or possibly other unmeasured confounders, and that such biases may explain, at least in part, non-specific effects of vaccines that appear to depend on which type of vaccine was delivered last.

In our analyses we used the SCCS method in which cases serve as their own controls with each case's observation period being divided into a pre-defined post-vaccination risk period or a control period. The method was first developed to assess adverse reactions to vaccines and automatically controls for individual confounding variables such as clinical, behavioural or socio-economic factors that do not vary with time and, in the case of non-specific effect studies, may predispose to hospital admission for an infection and also determine when or if a particular vaccine is given (i.e. vaccinees being generally more healthy as described in the Dutch study) [7]. Unlike cohort studies in which residual bias and confounding may still be present even in adjusted analyses, our SCCS analyses is not affected by such biases. Moreover, in our study the comparison between the RI of infection after MMR given alone or concurrently with an inactivated vaccine was the result of a change in national policy that resulted in MMR being the last vaccine given in Period 1 and MMR plus an inactivated vaccine in Period 2. The minority of children who for reasons unknown did not adhere to the recommended schedule could be excluded from the analysis whereas in the cohort studies within the same birth cohort they comprised the comparator group.

Despite the advantages of the SCCS method there are limitations. Whilst we adjust for the major time-varying confounder of age, other time-dependent factors may operate, such as a temporary healthy vaccinee effect. However, this would be independent of vaccine given which is consistent with our findings. Vaccine deferral after an event that occurs close to the time of scheduled vaccination can lead to a small over-estimation of the RI when using the SCCS method [15]. Further work is required to assess this bias when using long risk windows, but any such bias would not be expected to have a differential affect in the two periods so should not affect the rRI estimates. Our study compares schedules using different time periods. Whilst the method is not affected by differing incidence between the periods there were some differences in the distribution of the type of infection such that the all infections analysis involved a different distribution of infections in the two periods. Also, the exclusions due to receipt of other vaccines in the second year of life (or MMR not given with PCV in Period 2) differs between periods. We did not validate the accuracy of any of the diagnostic codes used in the analysis but neither was code validation done in the Danish or US cohort studies and it seems unlikely that the specificity of the clinical coding in HES was so much lower than in these other studies as to mask a non-specific effect. Indeed, HES codes were recently used to assess the impact of PCV7 vaccination on a range of non-specific infections and showed a clear relationship between expected specificity of the code for a pneumococcal-attributable infection and magnitude of impact [16]. In the UK national immunisation schedule no booster dose of DTaP is offered in the second year of life so we were unable to assess the specific effect of this inactivated vaccine on the risk of heterologous infections.

In conclusion our SCCS study provides no evidence to support the hypothesis that inactivated vaccines given on their own, or concurrently with a live vaccine, increase the risk of a non-targeted infection compared with administration of a live vaccine on its own, nor that MMR vaccine on its own decreases the risk. While our study was conducted in a high income setting and cannot necessarily be extrapolated to resource poor settings with high mortality, it is important that there is objective evaluation of the potential for bias and confounding in observational studies wherever they are conducted and recognition that this may still be present when using conventional cohort or case control methods despite adjustment for measured potential confounders.

5. Ethical permissions

Public Health England is able to process identifiable data under Regulation 3 of The Health Service (Control of Patient Information) (Secretary of State for Health, 2002). This is for purposes related to communicable diseases and other risks to public health and includes the delivery, efficacy and safety of immunisation programmes and adverse reactions to vaccines and medicines. To

obtain the CHIS immunisation data permissions were obtained from each PCT's Caldicott Guardian.

Author contributions

EM, NA and JS conceived the study. EM. NA and JS designed the study with input from ST and JW. JS extracted the data. NA analysed the data. JS, ST and JW developed code lists. NA, EM and JS drafted the paper. All authors were involved in the revision and approval of the final content before submission.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.059.

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